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Authors and their affiliations:

Hamilton Morrin [1]

Ton Fang [1];

Donald Servant [2];

Dag Aarsland [3,4]

Anto P. Rajkumar [3,4]

[1] Guy's hospital, King's College London, Great Maze Pond, London-SE1 9RT, UK

[2] South London and Maudsley NHS Foundation Trust, Bethlem Royal Hospital, Monks Orchard Road, Beckenham- BR3 3BX, UK

[3] Department of Old Age Psychiatry, Institute of Psychiatry, Psychology, & Neuroscience, King's College London, 16, De Crespigny Park, London-SE5 8AF, UK

[4] Mental Health of Older Adults and Dementia Clinical Academic Group, South London and Maudsley NHS foundation Trust, 115, Denmark Hill, London-SE5 8AZ, UK

Corresponding author:

Dr. Anto Praveen Rajkumar Rajamani,

M.D., D.N.B., M.R.C.Psych., Ph.D., Ph.D.,

Clinical Lecturer,

Department of Old Age Psychiatry,

Institute of Psychiatry, Psychology, & Neuroscience,

King's College London,

16, De Crespigny Park,

London - SE5 8AF, United Kingdom.

Email: Anto.Rajamani@kcl.ac.uk

Phone: +44 (0) 2078480508

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Abstract

Background: Pharmacological interventions for Lewy body dementia (LBD), especially for its non-cognitive symptoms, are limited in their efficacy and tolerability. Clinicians are often uncertain about non-pharmacological interventions and their efficacy in managing cognitive and non-cognitive symptoms of LBD. Therefore, we aimed to systematically review existing literature on non-pharmacological interventions for people with LBD.

Methods: We carried out a systematic search using six databases. All human studies examining impact of any non-pharmacological intervention on LBD were assessed for cognitive, physical, psychiatric, and quality-of-life outcomes. Study quality was assessed by effective public health practice project quality assessment tool for quantitative studies and the CARE criteria checklist.

Results: Prevailing evidence supporting the efficacy of non-pharmacological interventions is weak. We screened 1647 papers. Fifteen studies (N=61) including 11 case reports were found eligible for this systematic review. Interventions and reported outcomes were heterogeneous. Deep brain stimulation of the nucleus basalis of Meynert reportedly confer cognitive benefit. Electroconvulsive therapy and repetitive transcranial magnetic stimulation have been reported to ameliorate depressive symptoms. Transcranial direct current stimulation was observed to improve attention. Exercise-based interventions reportedly improve various clinically important outcomes. Spaced retrieval memory training and environmental intervention for ‘mirror sign’ have also been reported.

Conclusions: Several non-pharmacological interventions have been studied in LBD. Although evidence supporting their efficacy is not robust, prevailing preliminary evidence, and limitations of available pharmacological interventions indicate the need to consider appropriate non-pharmacological interventions, while planning comprehensive care of LBD

patients. Larger trials evaluating the efficacy of non-pharmacological interventions for LBD are needed.

Introduction

Lewy body dementia (LBD) is the second most prevalent form of neurodegenerative dementia. The term LBD encompasses two overlapping clinical syndromes, dementia with Lewy bodies (DLB) and Parkinson's disease dementia (PDD), which are conservatively estimated to contribute to 4.2-7.5% (Vann Jones and O'Brien, 2014) and 3.1-4.1% (Aarsland *et al.*, 2005) of all dementia, respectively. Notably, it has been reported that caregivers of people with DLB experience greater distress because of behavioral symptoms than in Alzheimer's dementia (AD) (Svendsboe *et al.*, 2016). Compared with other forms of dementia, LBD patients display an increased risk of mortality (Oesterhus *et al.*, 2014), earlier nursing home admissions (Rongve *et al.*, 2014), raised risk of falling (Komatsu, 2013), and reduced quality of life (Figari-Jordan *et al.*, 2012). Therefore, whilst LBD is not as common as AD, its relative burden on service users, their caregivers, and society is substantial.

Although much work has gone into the development of pharmacological therapies for LBD (Stinton *et al.*, 2015), as yet there are no disease-modifying treatments available. Management of neuropsychiatric symptoms in people with LBD is challenging. Recurrent well-formed visual hallucinations and delusional beliefs are common in LBD, but parkinsonism and severe neuroleptic sensitivity mandate minimizing use of antipsychotics. Limitations of available pharmacological interventions for LBD, especially for non-cognitive symptoms, include lack of high quality evidence for their efficacy (Stinton *et al.*, 2015), poor tolerability, and the potential risks of serious adverse effects. Hence, non-pharmacological interventions often play an important role in clinical management of people with LBD. Systematic research evaluating non-pharmacological interventions for LBD is sparse, and pertinent prevailing evidence is not readily available to interested clinicians. A recent systematic review has reported the impact of exercise therapy in LBD (Inskip *et al.*, 2016), but it did not include other non-pharmacological interventions for LBD, such as transcranial

direct current stimulation (tDCS) (Elder *et al.*, 2016), deep brain stimulation (DBS) (Barnikol *et al.*, 2010; Freund *et al.*, 2009), electroconvulsive therapy (ECT) (Takahashi *et al.*, 2009), or repetitive transcranial magnetic stimulation (rTMS). Updated knowledge regarding these non-pharmacological interventions may help clinicians to formulate comprehensive care plans for people with LBD. Therefore, we aimed to carry out the first comprehensive systematic review of the efficacy of all reported non-pharmacological interventions for cognitive and non-cognitive symptoms of LBD.

Methods

Study design

The protocol of this systematic review has been registered (PROSPERO protocol registration number: CRD42016049642), and is available online (www.crd.york.ac.uk/PROSPERO/).

Inclusion criteria

We employed broad inclusion criteria, and considered all eligible original studies regardless of their quality or design. (i) *Population***:** Studies investigating individuals of any gender, age and ethnicity with a clinical diagnosis of LBD were considered. Therefore, studies focusing on treatment of individuals with Parkinson's disease (PD) without dementia were not included. Additionally, studies which assessed an intervention in any form of dementia without separately reporting outcomes for LBD were not included. These studies were not included because of prior publication of comprehensive systematic reviews on non-pharmacological interventions for people with PD (Hindle et al., 2013) and for behavioral symptoms of dementia (Abraha et al., 2017). Animal studies were not included. (ii) *Interventions:* Studies investigating any non-pharmacological intervention for LBD were included. These included: physical and occupational therapy, exercise, social interaction, cognitive therapy, mindfulness, behavioral therapy, bright light therapy, tDCS, deep brain

stimulation, ECT, rTMS, music therapy, and other potential alternative therapies. These interventions were included regardless of whether they were acute or long-term. (iii) *Comparison*: No restrictions were applied. (iv) *Outcomes*: No restrictions were applied in order to avoid excluding relevant studies.

Search strategy

A systematic search was performed in December 2016 using the following six databases: MEDLINE, PsycINFO, CINAHL, EMBASE, Cochrane Central Register of Controlled Trials, and OpenGrey. The search strategy was comprised of both 'Population' AND 'Intervention' terms. These terms were searched in titles and abstracts of papers and grey literature. 'Comparison' and 'Outcome' terms were not used to ensure better search sensitivity. The population search terms used were: ('Parkinson*' AND 'dementia') OR ('Lewy' AND 'dementia').The intervention search terms used were: 'exercise' OR 'physical therapy' OR 'occupational therapy' OR 'social interaction' OR 'cognitive therapy' OR 'cognitive treatment' OR 'mindfulness' OR 'behavio?ral therapy' OR 'behavio?ral treatment' OR 'bright light therapy' OR 'pet therapy' OR 'education*' OR 'music therapy' OR 'transcranial direct current stimulation' OR 'transcranial magnetic stimulation' OR 'deep brain stimulation' OR electroconvulsive therapy' OR 'alternative therapy' OR 'non-pharmacological treatment' OR non-pharmacological intervention' OR 'non-pharmacological approach'. We did not specify any language limits, and we included non-English articles in the search strategy. However, only one non-English paper was identified as relevant (Fujiwara *et al.*, 2004).

Study selection

Screening followed several steps, the first of which was merging of duplicates using Mendeley Desktop 1.17.1 (Mendeley Ltd., London, UK). After this, papers with titles unrelated to dementia or PD were excluded, with subsequent exclusion of papers with abstracts which did not mention the use of any non-pharmacological intervention. This was

followed by exclusion of full text articles found to be ineligible, more specifically this involved excluding: articles focused on interventions for PD excluding or not controlling for PDD, articles focused on interventions for dementia excluding or not controlling for LBD, and articles providing insufficient details on their methods or outcomes. Ultimately, full text articles assessed to be eligible by the authors were reviewed, with resulting suitable articles included in the systematic review.

Quality assessment

Quality and potential likelihood of bias of eligible studies were assessed using the CARE criteria checklist (Gagnier *et al.*, 2013) for case reports, and the Effective Public Health Practice Project (EPHPP) Quality Assessment Tool for Quantitative Studies (Thomas *et al.*, 2004) for trials. We did not find any eligible qualitative studies. Studies were second-marked by independent raters, with any scoring inconsistencies resolved through discussion.

Data extraction

For each study deemed eligible for inclusion, extraction of the following data categories took place. (i) *Study design*: Studies were either considered experimental (randomized control trials (RCT) and non-randomized control trials (NRCT), uncontrolled trials (UCT)), or observational (case reports, case series, cross-sectional, case-control, prospective or retrospective cohort). (ii) *Intervention or exposure*: Method, frequency, intensity and duration of each study's non-pharmacological intervention were assessed. (iii) *Cohort*: Cohort was classified by any combination of diagnosis, age, gender, living or not living in the community, Unified Parkinson's Disease Rating Scale (UPDRS) (Martinez-Martin *et al.*, 1994) or other mobility scores, Mini-mental State Examination (MMSE) (Folstein *et al.*, 1975) or other cognitive test scores, and medications being taken. (iv) *Outcome*: Outcomes were classified according to the measurement test or tool used, mean differences between groups, effect sizes,

confidence intervals (CI), and statistical difference between groups, if such data were available.

Data synthesis

Studies were initially grouped on the basis of types of employed non-pharmacological interventions. They were regrouped on the basis of outcomes relevant to cognitive, neuropsychiatric, and motor symptoms of LBD. We assessed the levels of evidence using guidelines from the Oxford center for Evidence-Based Medicine (OCEBM-Levels-of-Evidence-Working-Group, 2011).

Results

Identified studies

Figure 1 outlines the study selection process in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) format. A joint search of EMBASE, MEDLINE, and PsycINFO unveiled 2171 papers. A further 1075 papers were found on CINAHL, whilst 323 were found on Cochrane Central Register of Controlled Trials, and 26 were found on OpenGrey. The 15 eligible articles included a single-blind randomized controlled trial (RCT) that included only four people with PDD (Telenius *et al.*, 2015), three uncontrolled trials (UCT) (Elder *et al.*, 2016; Rochester *et al.*, 2009; Takahashi *et al.*, 2009), and eleven case reports (Barnikol *et al.*, 2010; Ciro *et al.*, 2013; Dawley, 2015; Freund *et al.*, 2009; Fujiwara *et al.*, 2004; Gil-Ruiz *et al.*, 2013; Hayden and Camp, 1995; Kim *et al.*, 2017; Loher *et al.*, 2002; Rasmussen *et al.*, 2003; Tabak *et al.*, 2013).

Quality of included studies

When assessing quality of experimental trials, all four identified studies received weak or moderate global rating on the EPHPP quality assessment tool (see supplemental digital content (SDC)-1 attached to the electronic version of this paper at

http://journals.cambridge.org/ipg). Failure to control for confounders was a common limitation. In the case of exercise interventions, blinding is difficult to achieve because of the nature of intervention. Case report quality also varied, ranging from 11/28 (Barnikol *et al.*, 2010) to 23/28 (Dawley, 2015) on the 2016 CARE criteria checklist (See SDC-2). Despite five case reports scoring 20/28 or greater, one should note that case reports are inherently susceptible to selection, detection, and reporting biases. This may skew perception of efficacy, especially when outcomes from several case reports are assessed as a group.

Participant characteristics

In total, 61 individuals with LBD were included in this review. There were 31 with PDD, 22 with DLB, and 8 individuals, who are only described as having LBD. Table 1 presents further details of the individuals with LBD. Notably, the same individual has been assessed in two case reports for different outcomes following the same intervention (Barnikol *et al.*, 2010; Freund *et al.*, 2009) and thus has been assessed as a single person. Data on four PDD patients were obtained from a systematic review (Inskip *et al.*, 2016) due to primary data being reported as an average across 170 dementia patients (Telenius *et al.*, 2015). Participants were predominantly men (57.4%), and mean age was 70.3 years (95% CI 64.8-75.8). Scores indicating baseline cognitive function were reported for various tests including MMSE (n=44, mean=2.0, SD=13.8), and Montreal Cognitive Assessment (MoCA) (Nasreddine *et al.*, 2005) (n=14, mean=19.9, SD=13.0). Years since dementia onset was reported only in six studies (n=22, mean=2.4, SD=4.3). Five studies have reported years since onset of PD (n=18, mean=7.8, SD=10.1). In most studies, individuals took neuropsychiatric medications during the intervention period. However, two studies did not report whether participants were also taking medication (Rochester *et al.*, 2009; Takahashi *et al.*, 2009).

Efficacy of ECT

The highest level of evidence for benefits of ECT in treating depressive symptoms of LBD comes from the uncontrolled study in which the Hamilton Depression Rating Scale (HDRS) score (Hamilton, 1960) was observed to decrease significantly ($p<0.005$) from 38.0 (SD=5.8) to 15.0 (SD=9.6) (Takahashi *et al.*, 2009) (Table 2). The evidence for improvement of psychotic symptoms in people with LBD following ECT is limited, with one case series indicating reduction in hallucinations following ECT in two out of seven individuals with LBD (Rasmussen *et al.*, 2003) and another case report observing reduction in hallucinations and paranoid delusions following ECT (Fujiwara *et al.*, 2004) (See SDC-3).

Efficacy of DBS

A case report examining the effects of bilateral stimulation of the subthalamic nucleus (STN) and the nucleus basalis of Meynert (NBM) in PDD has supported the efficacy of DBS in treating cognitive deterioration (Freund *et al.*, 2009) (Table 3). Improvements in Auditory Verbal Learning and Memory Test (AVLT) (Lezak *et al.*, 2012) and other tests of cognitive functions have been reported (Table 3). A case report has reported minor improvement in Beck Depression Inventory (BDI-II) scores in a PDD patient following DBS of both STN and NBM (Freund *et al.*, 2009). Whilst the efficacy of DBS for motor symptoms of PD is well established (Baizabal-Carvallo and Alonso-Juarez, 2016), there is less evidence for its effect in LBD specifically. A case series has reported motor benefits of DBS in LBD. Improvements in UPDRS motor scores were observed following bilateral STN DBS. However, motor improvements lasted only 2-3 years in four individuals with LBD (Kim *et al.*, 2017) (See SDC-4).

Efficacy of rTMS

An uncontrolled study evaluating the efficacy of rTMS to treat depressive symptoms in people with LBD has reported statistically significant reduction of HDRS scores ($p<0.005$)

following rTMS (Takahashi *et al.*, 2009). The study has reported reduction of HDRS scores from 24.0 (SD=8.0) before the intervention to 11.0 (SD=5.9) after the intervention (Table 2). The efficacy of rTMS in treating other symptoms of LBD has not been evaluated systematically so far (See SDC-3).

Efficacy of tDCS

Evidence supporting efficacy of tDCS in ameliorating cognitive symptoms of LBD comes from an uncontrolled study in which 13 patients underwent stimulation of the left dorsolateral prefrontal cortex (Table 2). Performance of attention and visuoperceptual tasks was assessed before and after treatment, with percentage of correct answers and the mean reaction time for digit vigilance being seen to improve significantly (Table 2). However, changes in visuoperceptual task performance were not statistically significant (Elder *et al.*, 2016). There has not been any study evaluating the efficacy of tDCS in managing non-cognitive symptoms of LBD (See SDC-3).

Efficacy of physical exercise

Physical exercise is the most studied psychosocial intervention in people with LBD. Evidence supporting the benefits of exercise on cognition in PDD comes from a case report presenting an eight-week program of stationary cycling. Improvements in executive functions were observed using MoCA and PD cognitive rating scale (Pagonabarraga *et al.*, 2008). Exercise has been reported to increase mood and cognition (UPDRS part I) scores, and to reduce the time needed to complete color trails tests 1 and 2 (Messinis *et al.*, 2011; Tabak *et al.*, 2013) (Table 4). Of all non-pharmacological interventions for motor symptoms of LBD, exercise-based interventions have the best available evidence supporting their efficacy. However, there has not been any trial exclusively recruiting people with LBD. A subset of PDD patients (n=4) in a RCT, where participants undergoing the high intensity functional exercises program (Littbrand *et al.*, 2006) were compared with a light activity control, has provided

evidence for minor improvements in sit-to-stand function and habitual and maximal gait speed. Exercise may improve balance, measured by the Berg balance scale (Inskip *et al.*, 2016; Telenius *et al.*, 2015) (See SDC-5).

Other non-pharmacological interventions

Spaced retrieval memory training has been attempted as an intervention in PDD (n=2), though only one participant was able to successfully complete motor and motor-verbal tasks at final recall testing (Hayden and Camp, 1995). Additionally, one case report observed amelioration of 'mirror sign' associated with LBD, following an environmental intervention (Gil-Ruiz *et al.*, 2013).

Discussion

This systematic review is the first to comprehensively assess the efficacy of all reported non-pharmacological interventions in people with LBD, and it conformed to the PRISMA guidelines (Moher *et al.*, 2009). Table 5 summarizes the best available evidence for the efficacy of non-pharmacological interventions in treating various symptoms of LBD. The best available evidence supporting efficacy of non-pharmacological interventions is not robust. Currently available studies are small in scale. They often lack appropriate controls, and most of them have not accounted for potential confounding factors. Because of the lack of data homogeneity, secondary to the varying interventions assessed, and low quality of available literature, we could not perform meta-analysis. However, this preliminary evidence, together with the limitations of currently available pharmacological interventions, indicate the need to consider potential non-pharmacological interventions while planning comprehensive clinical care of people with LBD, and to plan pertinent research in future.

ECT is a non-pharmacological intervention that is readily available to many specialist psychiatric services treating people with LBD. Whilst ECT has been associated with transient

cognitive deficits in late-life depression, current evidence does not suggest long-term deleterious effects on cognition (Kumar *et al.*, 2016). Furthermore, a systematic review of the effects of ECT in PD and depression found depression improving in 93.1% of patients, with 94% remaining free from cognitive decline (Borisovskaya *et al.*, 2016). Extrapolating this evidence may support the safety of ECT in people with LBD. However, only one of three studies assessing ECT in LBD reported significant improvement in depression, and the study did not report post-ECT cognitive test results (Takahashi *et al.*, 2009). Though there has not been any study suggesting hastening of cognitive decline by ECT in LBD, there is a need for studies investigating long-term cognitive effects of ECT in people with LBD. Considering the efficacy of ECT in ameliorating severe depression and psychosis in older people with PD, ECT may be a potential treatment option for people with LBD, especially those who do not tolerate pharmacological interventions, with severe neuropsychiatric symptoms leading to active risks to self and others. The need for large robust trials evaluating the efficacy of ECT in treating such neuropsychiatric symptoms in LBD cannot be overemphasized.

Similarly, significant improvement of depressive symptoms in people with DLB following rTMS has been reported, but the report did not mention their post-rTMS cognitive functioning (Takahashi *et al.*, 2009). A recent meta-analysis has found rTMS to be superior to sham-rTMS in reducing depressive symptoms in people with PD, with antidepressant effects similar to that of selective serotonin reuptake inhibitors, and concurrent improvement in motor function (Xie *et al.*, 2015). Another systematic review has found rTMS to have no significant impact on cognition (Lage *et al.*, 2016). There has not been any double blind RCT evaluating the efficacy and safety of rTMS in reducing depressive symptoms in people with LBD, despite the need for such a trial. Whilst attentional improvements have been reported in people with LBD following tDCS, it is important to note that removal of outliers could have influenced the results (Elder *et al.*, 2016). Anodal tDCS over the prefrontal cortex has

previously shown efficacy in improving executive functions in people with PD (Boggio *et al.*, 2006; Cappon *et al.*, 2016; Pereira *et al.*, 2013). Hence, the efficacy of tDCS on executive functions of people with LBD requires further systematic investigation.

DBS involves an invasive neurosurgical procedure, and is therefore not feasible in many psychiatric settings treating people with LBD. Whilst DBS is used clinically for medication-refractory motor symptoms in PD, PDD is often considered a contraindication in DBS, partially due to the risk of postsurgical cognitive decline, particularly upon STN stimulation (Massano and Garrett, 2012). However, this systematic review identified four case reports reporting benefits of DBS in PDD. Freund *et al.* suggest that cognitive improvements observed in their patient were due to the effects of stimulating residual cholinergic projections and cell bodies in NBM (Freund *et al.*, 2009). Whilst it is not clear if NBM DBS alters progression of LBD, preclinical studies have suggested possible disease modifying mechanisms such as increased secretion of nerve growth factor (Hotta *et al.*, 2009) and enhanced neurogenesis (Jeong *et al.*, 2014). We came across two ongoing RCTs (Foltynie, 2017; Godefroy *et al.*, 2017) evaluating the efficacy of NBM DBS to treat cognitive symptoms of DLB. Results of these trials have not been published so far. Due to the nature of the intervention, difficulties in obtaining informed consent, and the likelihood of end-stage complications, it is important to consider on an individual basis whether DBS can be justified as a treatment option, particularly for those with moderate or severe LBD.

Several physical, cognitive, and quality of life outcome improvements have been reported in people with LBD receiving exercise-based interventions. Post-intervention increase in gait speed of 0.2 m/s or more has been reported in four studies, and this exceeds reported moderately clinically significant change of 0.14 m/s in PD cohorts (Hass *et al.*, 2014). A large clinically important effect in UPDRS section II scores following stationary cycling intervention has been reported (Tabak *et al.*, 2013). A 50m improvement in six-

minute walk test indicates moderately clinically significant change in geriatric populations, and an 82m improvement has been reported in a DLB patient following an exercise-based intervention (Dawley, 2015; Inskip *et al.*, 2016; Steffen and Seney, 2008). There is currently level 4 evidence to support the efficacy of exercise-based interventions to improve cognition, activities of daily living, motor symptoms, and depressive symptoms in people with LBD. Although the prevailing evidence is not robust, practicability, potential benefits, and minimal risk for serious adverse effects indicate the need to include exercise-based interventions in the comprehensive clinical care of people with LBD. The importance of further research on this topic cannot be overemphasized. Efficacy of other psychosocial interventions including psychoeducation and carer-based interventions has not been systematically investigated in LBD, and there is urgent need to design pertinent trials.

Studies evaluating non-pharmacological interventions for LBD are few, and they do not provide high-level evidence. Apart from the evidence supporting the use of acetylcholinesterase inhibitors for the management of cognitive symptoms of LBD, high-level evidence for the efficacy of available pharmacological interventions in people with LBD are also sparse (Stinton *et al.*, 2015). Considering the magnitude of burden on people with LBD, and on their caregivers, there is a clinical need to formulate individualized comprehensive care plans including both pharmacological and non-pharmacological interventions. There is an urgent need to expand pertinent evidence base. Among the 122 full-text articles that were identified, 86 (70.5%) were considered ineligible because of their exclusion of or failure to control for PDD in PD cohorts, or for LBD in dementia cohorts. It is high time to reconsider the eligibility criteria excluding people with LBD, and to design trials specifically investigating people with LBD. Non-pharmacological intervention trials deal with unique methodological challenges (Boutron *et al.*, 2008). Special attention should be given to standardizing different components of the intervention, tailoring the intervention for

the needs of individual participants, describing the expertise of intervention providers, and the choice of an appropriate control group. Non-pharmacological interventions that have shown promise in the management of PD may be investigated in people with LBD (Hindle *et al.*, 2013). Ultimately, robust complex intervention trials evaluating the efficacy of combined pharmacological and non-pharmacological interventions are needed to develop comprehensive clinical guidelines for the management of people with LBD.

Conflict of interest declaration

All authors except Prof. Dag Aarsland do not have any competing interests to declare. Prof. Aarsland has received research support and/or honoraria from Astra-Zeneca, H. Lundbeck, Novartis Pharmaceuticals and GE Health, and serves as paid consultant for H. Lundbeck, Eisai, and Axovant.

Description of authors' roles

Hamilton Morrin and Anto P. Rajkumar conceived this study, and wrote the protocol for the systematic review. Hamilton Morrin, Ton Fang, and Donald Servant carried out the systematic review including the quality assessment of identified studies. Hamilton Morrin wrote the initial draft of the manuscript. All authors were involved in the critical revisions of the manuscript.

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Figure legend

Figure 1. PRISMA flow diagram of the systematic review

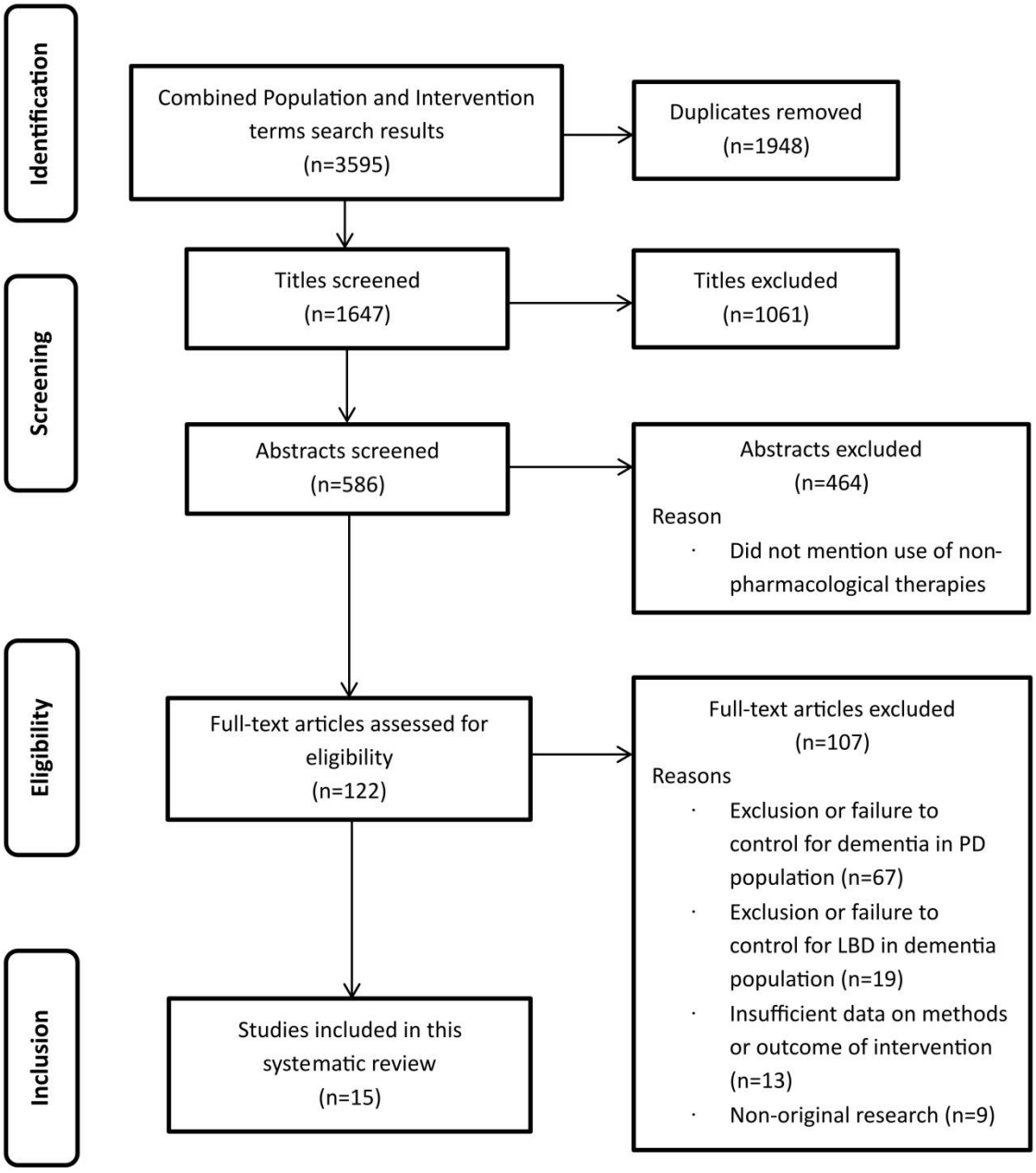

Table 1. Characteristics of individuals with LBD included in this systematic review

Citation	**Number of participants**	**Age Mean (SD)**	**Gender**	**Diagnosis**	**MMSE / other COG scores Mean (SD)**	**UPDRS Mean (SD)**	**Prescribed neuropsychiatric drugs**	**Residential Status**
Hayden *et al.*, 1995	2	72 (11.3)	2 M	PDD	23.5 (3.5); DRS: 110.5 (2.1)	NR	Non-specified medication for Parkinson's	Community
Loher *et al.*, 2002	1	75	M	PDD	22	Part III 31(ON), 52(OFF)	Carbidopa/levodopa; paroxetine	Community
Rasmussen *et al.*, 2003	7	73.6 (10.6)	2 M, 5 F	LBD	18.3 (7.4)	NR	Various antidepressants; antipsychotics; mood stabilisers; donepezil in 5; Carbidopa/levodopa in 2.	Case 1: Community
Fujiwara *et al.*, 2004	1	20	F	DLB	22	NR	Carbidopa/levodopa; cabergoline; quetiapine	Community
Takahashi *et al.*, 2009 (ECT)	8	71.6 (7.3)	1 M, 7 F	3 possible DLB, 5 probable DLB	NR	NR	At least 2 antidepressants; lithium carbonate; sodium Valproate (withdrawn prior to ECT)	NR
Takahashi *et al.*, 2009 (rTMS)	6	61.9 (9.2)	3 M, 3 F	5 suspected DLB, 1 probable DLB	NR	NR	NR	NR
Freund *et al.*, 2009; Barnikol *et al.*, 2010	1	71	M	PDD	CDT: 4; $AVLT_{sum}$: 12	NR	Dopaminergic medication	NR
Rochester *et al.*, 2009	9	74.9 (6.5)	9 M	PDD	22 (3.0)	Part III, 44 (7.2)	NR	Community

Gil-Ruiz *et al.*, 2013	1	85	F	Probable LBD	19	NR	Donepezil; escitalopram	Nursing home
Ciro *et al.*, 2013	1	73	F	DLB	12	NR	Citalopram; Rivastigmine; Rasagiline	Community
Tabak *et al.*, 2013	1	61	M	PDD	MoCA: 17	Part I: 11; Part II: 15	Carbidopa/levodopa	Community
Dawley, 2015	1	57	M	DLB	NR	NR	Carbidopa/levodopa; antidepressant; antipsychotic	Community
Telenius *et al.*, 2015	4	84.0 (10.0)	1 M, 3 F	PDD	16 (7.1)	NR	NR	Nursing home
Elder *et al.*, 2016	5	65.0 (7.7)	3 M, 2 F	DLB	20.6 (3.1); MoCA: 17.6 (3.7)	Part III 12.8 (5.6)	1 on cholinesterase inhibitors; all on anti-Parkinsonian medication	NR
Elder *et al.*, 2016	8	64.6 (8.2)	7 M, 1 F	PDD	22.0 (2.6); MoCA: 19.4 (2.5)	Part III 28.5 (9.4)	3 on antidepressants; all on anti-Parkinsonian medication	NR
Kim *et al.*, 2016	5	66.0 (1.9)	3 M, 1 F	PDD	21.6 (3.8)	Part III 19.4 (4.1) (ON), 25.7 (11.9) (OFF)	None on cholinesterase inhibitors; all on levodopa	Community

Data given as mean or individual values where appropriate**.** Figures rounded to one decimal place. Note that demographic data from Telenius *et al.* 2015 was unavailable for the four PDD participants and thus was acquired from a systematic review which had obtained results directly from the authors (Inskip *et al.*, 2016). AVLT–Auditory Verbal Learning and Memory Test; CDT–Clock Drawing Task; COG- cognitive assessment; DLB–Dementia with Lewy bodies; DRS–Mattis Dementia Rating Scale; ECT–Electroconvulsive therapy; F- Women; M- Men; MCI–Mild cognitive impairment; MMSE–Mini-mental state Examination score; MoCA–Montreal Cognitive Assessment; NR–Not Reported; PDD–Parkinson's Disease Dementia; rTMS–repetitive transcranial magnetic stimulation; UPDRS=Unified Parkinson's disease rating scale (Part I–Mood and cognition, Part II–Activities of daily living, Part III–Motor).

Table 2. Reported outcomes following electroconvulsive therapy, repetitive transcranial magnetic stimulation and transcranial direct current stimulation in people with Lewy body dementia (n=35)

Citation		Measure/Feature	Baseline	Outcome
ECT				
Rasmussen *et al.*, 2003	Case 1	MMSE (/30)	24	23-28
		HDRS	NR ("severe depression")	6-8
		Visual hallucinations	Intense and persistent	Reduction in intensity
	Case 2	MMSE (/30)	19	23
		HDRS	33	8
	Case 3	MMSE (/30)	4	4
		Visual hallucinations	Present	Markedly reduced for 2 weeks then recurred
	Case 4	MMSE (/30)	NR	6-19
		HDRS	NR ("severe depression")	18-27
	Case 5	MMSE (/30)	28	21
		HDRS	17	17 (mood reportedly improved)
	Case 6	Depression	Present	Temporarily improved
		Delusion	Prominent	Temporarily reduced
	Case 7	Depression (/30)	Present	Acute improvement
Fujiwara *et al.*, 2004	Clinical features		Insomnia, mild depression, hallucinations and delusions	Alleviation of depressed mood, hallucinations and delusions
Takahashi *et al.*, 2009	HDRS		38.0 (5.8)	15.0 (9.6)
rTMS				
Takahashi *et al.*, 2009	HDRS		24.0 (8.0)	11.0 (5.9)
tDCS				
Elder *et al.*, 2016	Choice Reaction Time - Correct Answers (%)		71.8 (28.3)	87.7 (20.9)
	Digit Vigilance - Mean Reaction Time (ms)		632.9	582.9

Figures rounded to one decimal place. ECT–Electroconvulsive therapy; HDRS- Hamilton Depression Rating Scale; MMSE–Mini-Mental State Examination; NR–Not reported; rTMS–Repetitive transcranial magnetic stimulation; tDCS–Transcranial direct current stimulation.

Table 3. Outcomes following deep brain stimulation in people with Lewy body dementia at time points relative to electrode implantation (n=7)

Citation	**Time of recording**	**ADL (UPDRS Part II)**		**Motor (UPDRS Part III)**		**MMSE**
		Off	On	Off	On	
Loher *et al.*, 2002	Preoperative	32	20	52	31	22
	3 months postoperative	26	18	40	21	17
	1 year postoperative	34	21	43	33	8
Kim *et al.*, 2016	Preoperative	NR	NR	49.9 (19.1)	36.4 (37.7)	21.6 (3.8)
	1 year postoperative	NR	NR	25.7 (11.9)	19.38 (4.1)[A]	23.5 (2.4)[B]
Citation	**Time of recording**	**$AVLT_{sum}$, (No. of words)**	**CDT (points)**	**TMT-A (minutes: seconds)**	**Vfl_{sum} (No. of words)**	**BDI-II (points)**
Freund *et al.*, 2009; Barnikol *et al.*, 2010	Preoperative	12	4	05:24	23	26
	Bilateral stimulation of STN, 12 weeks postoperative	15	7	03:02	30	20
	Bilateral stimulation of STN + NBM, 16-23 weeks postoperative (mean of 4 tests)	23	8.5	02:29	26	20.8
	Isolated stimulation of STN + sham stimulation of NBM, 24 weeks postoperative	11	6	04:10	14	24
	Bilateral stimulation of STN + NBM, 24-29 weeks postoperative (mean of 3 tests)	21.3	8	03:44	24.7	19.7

Numbers within brackets indicate standard deviations. Figure rounded to one decimal place. ADL–Activities of daily living; AVLT–Auditory Verbal Learning and Memory Test; BDI-II–Beck's depression inventory; CDT–Clock drawing test; DBS–Deep brain stimulation; MMSE–Mini-Mental State Examination; NBM–Nucleus basalis of Meynert; NR–Not reported; On/Off–On/Off phase of levodopa-related motor fluctuation; STN–Subthalamic nucleus; TMT-A–Trail making test part A; UPDRS–Unified Parkinson's Disease Rating Scale; Vfl–Verbal fluency. [A]Average of four patients as 'case 5' ceased medication following surgery; [B]Average of four patients as MMSE was not measured in 'case 4' post-intervention. Note that for results from Kim *et al.,* 2016, 'case 3' was too dysarthric for assessment at 12 months so data from 6 months postoperative have been used instead of 12 months.

Table 4: Reported outcomes in studies assessing the impact of physical activity in people with Lewy body dementia (n=16)

Citation	**Measure**	**Exercise**		**Control**	
		Baseline	**Outcome**	**Baseline**	**Outcome**
Rochester *et al,.* 2009	Habitual gait speed (m/s)	0.7 (0.2)	0.9 (0.2)	NA	NA
	Dual task gait speed (m/s)	0.7 (0.2)	0.7 (0.2)	NA	NA
	Single task cadence (steps/minute)	98.7 (6.7)	104.2 (7.2)	NA	NA
Ciro *et al.,* 2013	Single chair stand - COPM performance	1	5	NA	NA
	Single chair stand - COPM satisfaction	1	6	NA	NA
Tabak *et al.*, 2013	2 Minute Walk Test - Single task (m)	100.6	129.5	NA	NA
	2 Minute Walk Test - Dual task (m)	60.7	102.7	NA	NA
	Functional Gait Assessment (/30)	13	23	NA	NA
	MoCA (/30)	17	24	NA	NA
	PDCRS (/134)	55	70	NA	NA
	Color Trails Test 1 (s)	277	118	NA	NA
	Color Trails Test 2 (s)	360	156	NA	NA
	UPDRS I (/16)	11	1	NA	NA
	UPDRS II (/52)	15	6	NA	NA
	PDQ-39 (/156)	83	70	NA	NA
Dawley 2015	30s sit-to-stand	4	8	NA	NA
	Habitual gait speed - 7.6m walk test (m/s)	0.8	1.4	NA	NA
	6 Minute Walk Test - Single task (m)	480.4	562.1	NA	NA

	Balance - MiniBESTest (/28)	21	25	NA	NA
	Balance - Timed Up & Go Test (s)	15.5	9.1	NA	NA
	G-code: Mobility (% impairment)	67	40	NA	NA
Telenius *et al.*, 2015	30s sit-to-stand	5.5 (0.5)	8 (0.0)	5.5 (2.3)	6 (2.0)
	Habitual gait speed – 6m walk test (m/s)	0.4 (0.0)	0.5 (0.2)	0.5 (0.1)	0.4 (0.1)
	Maximal gait speed – 6m walk test (m/s)	0.8 (0.3)	1.0 (0.5)	0.8 (0.1)	0.8 (0.3)
	Berg balance scale (/56)	23[A]	27[A]	35.5 (6.5)	35.5 (5.5)
	Activities of daily living –Barthel index (/20)	12 (1)	12[B]	11.5 (0.5)	13.5 (0.5)

Figures rounded to 1dp. COPM–Canadian Occupational Performance Measure; MoCA–Montreal Cognitive Assessment; NA–Not Applicable; PDCRS–Parkinson's Disease Cognitive Rating Scale; PDQ-39–Parkinson's Disease Questionnaire-39; UPDRS–Unified Parkinson's Disease Rating Scale (I–Mood & Cognition, II–Activities of Daily Living). [A]Result only reported for first intervention participant; [B]Result only reported for second intervention participant.

Table 5: Oxford Centre for Evidence-Based Medicine levels of evidence for the efficacy of non-pharmacological interventions for various symptoms of Lewy body dementia

Symptoms		**Non-pharmacological intervention**	**Highest level of evidence**	**Citation for highest level of evidence**
Cognitive		DBS	5	Freund, *et al.*, 2009
		tDCS	3	Elder, *et al.*, 2016
		Exercise	4	Tabak, *et al.*, 2013
Activities of daily living		DBS	5	Loher, *et al.*, 2002
		Exercise	4	Tabak, *et al.*, 2013
Neuropsychiatric	Depression	DBS	5	Freund, *et al.*, 2009
		ECT	4	Takahashi, *et al.*, 2009
		rTMS	4	Takahashi, *et al.*, 2009
		Exercise	4	Tabak, *et al.*, 2013
	Hallucinations	ECT	4	Rasmussen, *et al.*, 2003
	Delusions	ECT	5	Fujiwara, *et al.*, 2004
Motor		DBS	4	Kim, *et al.*, 2016
		Exercise	4	Telenius, *et al.*, 2014

'Motor' refers to Parkinsonian motor symptoms such as bradykinesia and resting tremor. DBS–deep brain stimulation; ECT–electroconvulsive therapy; rTMS–repetitive transcranial magnetic stimulation; tDCS–transcranial direct current stimulation; Level of evidence 3- Non-randomized controlled cohort/follow-up study; Level of evidence 4- Case-series, case-control studies, or historically controlled studies; Level of evidence 5- Mechanism-based reasoning